Remarks

Claims 1-20 were pending in the application. Claims 19 and 20 are cancelled. Claims 1-18, 21 and 22 are currently pending in the application.

Claim 1, as amended above, now recites a method for producing autologous thrombin, where the steps of the claimed method result in "a thrombin preparation comprising 80-90% of prothrombin-thrombin proteins, no detectable fibrinogen and 20-30% of baseline levels of anti-thrombin III (ATIII)." Support for the amendment is found in original claim 20. No new matter is added by the amendment.

The present invention relates to a point-of-care method for obtaining autologous thrombin directly from whole blood without the need for the clinically accepted plasma isolation step.

Rejection under 35 U.S.C. §103

Claims 1, 2, 3, 7-15 and 21 are rejected under 35 U.S.C. §103(a) as being unpatentable over Gray et al. (US 4,680,177) in view of Cochrum et al. (US 5, 773,033). Specifically, the Office Action asserts that one of skill in the art would have been motivated to substitute different methods of precipitation for cryoprecipitation in the method of Gray et al. with a reasonable expectation of success because Cochrum et al. teaches that these are art recognized equivalents for forming precipitates from blood. Applicants respectfully disagree.

The method as claimed herein is directed to a method for the production of an autologous thrombin that is virtually free of fibrinogen and contains significantly reduced levels of thrombin inhibitor, AT III. A major concern in preparing autologous thrombin directly from whole blood is the uncertainty attendant with the level of thrombin inhibitors remaining following precipitation.

The teachings of Gray et al. and Cochrum et al. have been discussed previously. Gray et al. is cited in the Office Action for its teaching that anticoagulated whole blood can be fractionated by cryoprecipitation. Gray et al. teaches that a preferred process for isolation of certain blood components that are present in low concentrations and are difficult to isolate is a cryoprecipitation step, that is, by freezing to low temperature and then thawing at 0°C to 4°C. (col. 4, lines 30-33). Freezing and thawing is a gentler treatment than chemical precipitation with an agent such as ethanol. One of skill in the art would likely not substitute a chemical method of precipitation for cryoprecipitation.

This teaching of Gray et al. is combined with the teachings of Cochrum et al., in particular, a reference in Cochrum et al. to an 1987 article in Laryngoscope that describes "...highly concentrated fibrinogen obtained by cryo-precipitation or by precipitation of fibrinogen with ethanol, centrifugation, or ammonium sulfate using saturated solution of purified ammonium sulfate." The teachings of Cochrum et al. relate to preparation of purified fibrinogen and are, therefore, completely inapposite to Applicants' method as currently claimed, which seeks to produce an autologous thrombin that is virtually free of fibrinogen. There is nothing in the cited references from which the person of skill in the art would conclude that a method suitable for the extraction of fibrinogen would be effective for the isolation of functional thrombin. Thus, Cochrum et al, does not remedy the deficiency in the teachings of Gray et al. The cited references are not combinable.

Blood fractionation methods are many and varied. The kind and conditions of precipitation affect the product obtained. Cryoprecipitation is not interchangeable with precipitation with a salt, such as ammonium sulfate, which is not interchangeable with precipitation with an organic material, such as ethanol. One cannot extrapolate a method for one protein to another unrelated protein. The Office Action position that optimization of conditions would be a matter of routine is unfounded. Because there is an infinite number of combinations and permutations of parameters (e.g. volume of starting material used, volume of precipitating agent or method used, temperature at which the method is performed, amount of contaminants/inhibitors remaining in product, etc.) one of skill in the art would ***not*** have had a

reasonable expectation of success in obtaining the desired end product simply by substituting one precipitation method for another. This is particularly true if other variables are introduced, for example, using whole blood as the starting material rather than plasma. Thus, there is no apparent reason why one of skill in the art would combine the teachings of Cochrum et al. and Gray et al. and to achieve Applicants' invention, as currently claimed.

Claims 1-4, 7-18 and 21-22 are rejected under 35 U.S.C. §103(a) as being unpatentable over Coelho et al. in view of Rock (US 4,359,463). According to the Office Action, it would have been obvious for one of skill in the art to modify the method of obtaining autologous thrombin, allegedly from whole blood, as taught by Coelho et al. by adding a commonly used anticoagulant as taught by Rock et al.

As Applicant has already established by its Declaration Under 37 C.F.R. 1.132 of Dr. Sherwin Kevy, 2007 Journal of The American Society of Extra-Corporeal Technology article by Vijay Kumar, and other documents, there is nothing in the prior art to substantiate the assertion that one of skill in the art, at the time of the Coelho et al. patent, would have read that document as teaching a method for the extraction of autologous thrombin by the direct precipitation of whole blood. Applicants respectfully point out that while the specification contains sufficient detail with regard to specific parameters of processing plasma (e.g., 9-10 ml plasma, 1 ml of 75mM calcium chloride and 2.0 ml of ethanol) similar details regarding parameters specific to the processing of whole blood are conspicuously absent. It is unlikely that one could extrapolate the same parameters to whole blood given that 40% of the volume of whole blood is cellular.

Furthermore, claim 1, as amended above, requires that the resulting autologous thrombin contain 80-90% of prothrombin-thrombin proteins, no detectable fibrinogen and 20-30% of baseline levels of anti-thrombin III (ATIII). None of the cited references teach such a product, nor can one claim that the autologous thrombin taught by Coelho et al. inherently meets those criteria given the lack of specifics provided by Coelho et al. for preparation of autologous thrombin using whole blood.

Claims 5 and 6 are rejected under 35 U.S.C. §103(a) as being unpatentable over Coelho et al. in view of Rock as applied to claims 1-4 and 7-18 and further in view of Sato et al. According to the Office Action, even though Coelho et al. does not teach anticoagulation of blood prior to use, it would have been obvious to do so based on the teachings of Rock et al.

Claims 5 and 6 depend from claim 1 and therefore, contain all the limitations of the independent claims. The disclosure of Coelho et al. does not teach or fairly suggest Applicants' claimed method for the reasons stated above and in previous responses.

Rock et al., describes a method for the stabilization of Factor VIII activity in whole blood or blood plasma by addition of a calcium-heparin solution, whereby calcium is restored to physiologic levels following anticoagulation of the blood with a calcium chelating anticoagulant. Rock et al. does not relate to the precipitation of either whole blood or plasma for the recovery of a coagulant material like thrombin. Rock et al. does not compensate for the deficiencies in the teachings of Coelho et al.

Claims 5 and 6 are rejected under 35 U.S.C. §103(a) as being unpatentable over Coelho et al. in view of Rock as applied to claims 1-4 and 7-18 and further in view of Sato et al. According to the Office Action, One of ordinary skill in the art would have been motivated to add mannitol to the ACD anticoagulant in the method of Coelho et al. because Sato et al. teaches that by adding mannitol to blood, the swelling of blood cells can be prevented during the preservation.

Sato et al. describes the benefit of reduced hemolysis by adding glycerin and mannitol to a blood preservation solution.

To the extent that both Rock et al. and Sato et al. relate to anticoagulant preparations commonly used in the art, but not to mixing of whole blood with a precipitating agent to obtain a supernatant containing a coagulant, they do not compensate for the deficiencies in the teachings of Coelho et al.

None of the references cited herein *either alone or in combination* teach or fairly suggest that autologous thrombin can be extracted from whole blood by precipitation of the whole blood without first performing a plasma isolation step. The ultimate solution of a previously intractable problem can indeed appear to become apparent in hindsight after the final successful step is taken. Yet that final step in this case was not taken by those who came before, and was clearly not "obvious" to contemporaries, based on the subsequent peer review and publication of Applicants' claimed method in the scientific literature.

Withdrawal of the rejection(s) under 35 U.S.C. §103(a) is respectfully requested.

In view of the above amendment and remarks, the claims are now in condition for allowance and reconsideration and prompt allowance are respectfully requested. The Examiner is invited to contact Applicants' Attorney at the telephone number given below if any further questions arise in connection with this Application.

Respectfully submitted,

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